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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/117,218	01/11/1999	SUSANNE M. BROWN	117-261	3436

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EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1632	14

DATE MAILED: 12/05/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/117,218	BROWN ET AL.	
	Examiner	Art Unit	
	Quang Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *13-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's amendment filed September 17, 2001 in Paper No. 13 has been entered. Claims 13-22 are pending in the present application and they are examined on the merits herein.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior office action.

Response to Amendment

The rejection of claims 13-22 under 35 U.S.C. 112, first paragraph is withdrawn in light of Applicants' amendment.

The provisional rejection of the pending claims of the present application as being obvious over claims of the co-pending Application No. 08/776,350 is maintained for the reasons set forth in the Office Action in Paper No. 10.

Claim Rejections - 35 USC § 102

Claims 13-20 remain rejected under 35 U.S.C. 102(e) as being anticipated by Martuza et al. (U.S. Patent No. 6,139,834 with the effective filing date of June 23, 1994) for the reasons already set forth in the previous Office Action in Paper No. 12.

The claims are drawn to a method of treating a non-neuronal cancer in a mammal, preferably a human, which method comprises the step of injecting a mammal intratumorally with an effective amount of a mutant herpes simplex virus which has been

modified in the γ34.5 gene such that the gene is non-functional, and wherein the mutant virus infects, replicates and lyses tumor cells of said non-neuronal cancer, thereby treating the non-neuronal cancer; the same method wherein said cancer is a primary or a metastatic tumor; or wherein the cancer is a mesothelioma, ovarian carcinoma, bladder cancer or melanoma; or wherein the mutant herpes simplex virus is a type I herpes simplex virus; or wherein the mutant herpes simplex virus has been modified within the BamH1 restriction fragment of the long terminal repeat of the viral genome, preferably the modification is a deletion of from 0.1 to 3 kb of the BamH1 restriction fragment of the long terminal repeat of the viral genome.

With respect to a method for killing tumor cells in a subject via intratumoral injection of mutant herpes simplex virus, Martuza et al. teach the delivery of a pharmaceutical composition comprising: (A) a herpes simplex virus vector that is altered in (i) the γ34.5 gene, and (ii) the ribonucleotide reductase gene; and (B) a pharmaceutically acceptable vehicle for said vector, such that said tumor cells are altered *in situ* by said vector, whereby said tumor cells are killed; the same method wherein said tumor cells are selected from the group consisting of melanoma cells, pancreatic cancer cells, prostate carcinoma cells, lymphoma cells, hepatoma cells and mesothelioma and epidermoid carcinoma cells (See the entire patent and particularly claims 1and 3). An exemplary mutant herpes simplex virus, G207, disclosed by Martuza et al. contains a 1-kB deletion in both copies of the γ34.5 gene within the BamH1 fragment of the long terminal repeat of the viral genome (See Figures 1, 2 and column 15, lines 36-45). The mutant herpes simplex virus can be derived from either

HSV-1 or HSV-2 (column 4, lines 20-22; column 7, lines 6-22; column 8, lines 5-7). The mutant herpes simplex virus can be administered to human and non-human animals suffering from tumors and neoplasms by direct intraneoplastic inoculation (column 11, lines 45-57). Moreover, the disclosed method for killing tumors and neoplasms is not necessarily limited to malignant brain tumor, such as astrocytoma, glioblastoma and others (column 11, lines 45-55; column 3, lines 61-67). Therefore, Martuza et al. clearly anticipate the instantly claimed invention.

It should be noted that the U.S. Patent No. 6,139,834 of Martuza et al. has an effective filing date of June 23, 1994 because of the supports found in column 3, lines 52-58; column 12, lines 6-7; column 15, lines 41-50 and other embodiments contained in the U.S. Patent No. 5,585,096 of Martuza et al.

Responses to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on September 17, 2001 in Paper No. 13 (pages 4-5) have been fully considered.

Applicants argued that the cited Martuzan patent failed to provide an enabling disclosure of the presently claimed method. Additionally, Applicants are uncertain why Examiner has relied on U.S. Patent No. 6,139,834 as opposed to either U.S. Patent No. 5,728,379 and/or U.S. Patent No. 5,585,096. Examiner respectfully finds Applicants' argument to be unpersuasive because Applicants have not provided any objective evidence showing that the cited Martuzan patent (U.S. Patent No. 6,139,834) failed to provide an enabling disclosure of the presently claimed method despite of the teachings

disclosed by Martuza set forth above. Applicants' attention is further directed to the claims of the issued U.S. Patent No. 6,139,834, as well as the title of the issued U.S. Patent Nos. 6,139,834 and 5,585,096 as "Replication-competent herpes simplex virus mediates destruction of neoplastic cells" (Please note that the title is not for the destruction of only to neuronal cancer cells). Examiner has relied on U.S. Patent No. 6,139,834 which is the prior art under 35 U.S.C. 102(e) as opposed to U.S. Patent No. 5,585,096 to clearly show that on the basis of the specification of the issued Patent No. 6,139,834, the instantly claimed invention has been anticipated by the teachings of Martuza as evidenced by the claims given in the issued U.S. Patent Nos. 6,139,834. It is further noted that the specification of the issued Patent No. 6,139,834 is the same as that of the issued Patent No. 5,585,096. With respect to the issue that why Examiner did not rely on the issued U.S. Patent No. 5,728,379, Applicants' comments are not germane or relevant to the stated rejection.

Applicants also argued that the U.S. Patent No. 6,139,834 fails to teach each and every aspect of the presently claimed invention. Examiner respectfully finds Applicants' arguments to be unpersuasive because Applicants fail to clearly point out specifically which element or aspect of the presently claimed invention that the issued U.S. Patent No. 6,139,834 allegedly fails to teach? Without any specifics, it is simply Applicants' opinion.

Applicants also argued that U.S. Patent No. 5,585,096 as well as U.S. Patent No. 6,139,834 fail to provide an enabling disclosure of the presently claimed invention. With respect to U.S. patent No. 6,139,834, Applicants further argued that the issued patent

only exemplifies the treatment of neuronal tumors and specifically gliomas. Examiner respectfully finds Applicants' arguments to be unpersuasive because once again Applicants fail to provide any objective evidence why the disclosures of the aforementioned issued patents are not enabled for the presently claimed invention, and yet claims specifically directed to a method of killing tumor cells (both neuronal and non-neuronal tumor cells) in a subject using a herpes simplex virus vector comprising an alteration in the γ34.5 gene have been issued. It should also be noted that claims of an issued U.S. Patent is presumed to be valid and that the enabled scope of an issued U.S. Patent is not limited by the exemplification. Furthermore, Applicants have not provided extrinsic evidence to show that one of ordinary skill in the art would not have recognized the Martuza reference does not teach the method as claimed.

Accordingly, claims 13-20 remain rejected under 35 U.S.C. 102(e) as being anticipated by Martuza et al. (U.S. Patent No. 6,139,834 with the effective filing date of June 23, 1994) for the reasons set forth above.

Claim Rejections - 35 USC § 103

Claims 13, 19-22 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Martuza et al. (U.S. Patent No. 6,139,834 with the effective filing date of June 23, 1994) in view of either MacLean et al. (J. Gen. Virol. 72:631-639, 1991, Cited previously) or Brown et al. (WO 92/13943 with a publication date of August 20, 1992; PTO-1449, IDS) and Markert et al. (Neurosurgery 32:597-603, 1993; IDS) for the reasons already set forth in the Office Action in Paper No. 12.

The claims are drawn to a method of treating a non-neuronal cancer in a mammal, preferably a human, which method comprises the step of injecting a mammal intratumorally with an effective amount of a mutant herpes simplex virus which has been modified in the γ34.5 gene such that the gene is non-functional, and wherein the mutant virus infects, replicates and lyses tumor cells of said non-neuronal cancer, thereby treating the non-neuronal cancer; the same method wherein the mutant herpes simplex virus has been modified within the BamH1 restriction fragment of the long terminal repeat of the viral genome, preferably the modification is a deletion of from 0.1 to 3 kb of the BamH1 restriction fragment of the long terminal repeat of the viral genome, more preferably the deletion is from 0.7 to 0.8 kb; and the same method wherein the mutant herpes simplex virus is strain 1716.

With respect to a method for killing tumor cells in a subject via intratumoral injection of mutant herpes simplex virus, Martuza et al. teach the delivery of a pharmaceutical composition comprising: (A) a herpes simplex virus vector that is altered in (i) the γ34.5 gene, and (ii) the ribonucleotide reductase gene; and (B) a pharmaceutically acceptable vehicle for said vector, such that said tumor cells are altered *in situ* by said vector, whereby said tumor cells are killed; the same method wherein said tumor cells are selected from the group consisting of melanoma cells, pancreatic cancer cells, prostate carcinoma cells, lymphoma cells, hepatoma cells and mesothelioma and epidermoid carcinoma cells (See the entire patent and particularly claims 1and 3). An exemplary mutant herpes simplex virus, G207, disclosed by Martuza et al. contains a 1-kB deletion in both copies of the γ34.5 gene within the

BamH1 fragment of the long terminal repeat of the viral genome (See Figures 1, 2 and column 15, lines 36-45). The mutant herpes simplex virus can be derived from either HSV-1 or HSV-2 (column 4, lines 20-22; column 7, lines 6-22; column 8, lines 5-7). The mutant herpes simplex virus can be administered to human and non-human animals suffering from tumors and neoplasms by direct intraneoplastic inoculation (column 11, lines 45-57). Moreover, the disclosed method for killing tumors and neoplasms is not necessarily limited to malignant brain tumor, such as astrocytoma, glioblastoma and others (column 11, lines 45-55; column 3, lines 61-67). Martuza et al. do not teach a method of killing tumor cells in a subject using the mutant herpes simplex virus wherein there is a deletion from 0.7 to 0.8 kb of the BamH1 restriction fragment of the long terminal repeat of the viral genome, or wherein the mutant herpes simplex virus is strain 1716.

Both MacLean et al. and Brown et al. disclose HSV-1 mutant 1716 and they both teach that strain 1716 contains a 759 bp deletion in the γ34.5 gene which is found within the BamH1 s fragment of the long repeat region of the viral genome (See abstract and Fig. 3 on page 634 of MacLean et al.; page 4, lines 16-31 in Brown et al.). The deletion is associated with the non-neurovirulence for strain 1716 comparing to the parental wild type strain.

Markert et al. teach a herpes simplex virus-1 called R3616 with decreased neurovirulence (See abstract) and the virus contains a 1kb deletion in the γ34.5 gene (page 598, column 1, bottom of third paragraph). Markert et al. further teach that R3616 possesses antineoplastic effects and it significantly prolonged average survival without

producing premature encephalitic deaths in a nude mouse intracranial glioma model (See abstract).

Accordingly, it would have been obvious to one of ordinary skilled in the art at the time of invention was made to substitute any of the mutant herpes simplex virus utilized in the method disclosed by Martuza et al. with mutant virus strain 1716 taught by MacLean et al. and Brown et al., and one of ordinary skilled in the art would have expected to successfully killing tumor cells in a subject via an intratumoral route of delivery. This is because it was well known in the art that mutant herpes simplex virus having a deletion in the γ34.5 gene has reduced non-neurovirulence and still possesses anti-neoplastic effects as exemplified by the teachings of Markert et al. and Martuza et al. Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Responses to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on September 17, 2001 in Paper No. 13 (pages 5-6) have been fully considered have been fully considered.

Applicants basically argued that the secondary references fail to cure the deficiencies of Martuza as cited in Applicants' arguments related in the rejection of claims 13-20 above. Applicants argued that the art taught away from the use of mutant HSV for treating non-neuronal tumor cells. Furthermore, Applicants argued that "the Martuza U.S. Patent No. 5,585,096 may be considered to provide guidance to one of

ordinary skill in the art to try mutated HSV on non-neuronal tumor cells however given the negative teaching in the art and the unsubstantiated and speculative statements in the U.S. Patent No. 5,585,096, the applicants believe the ordinary skilled person would not have thought it likely that non-neuronal cancer could be treated in the manner which is presently claimed". Examiner respectfully finds Applicants' arguments to be unpersuasive for the following reasons.

Firstly, with respect to Applicants' arguments related to the deficiencies of the primary reference of Martuza, they are not found to be persuasive for the reasons already stated above. Therefore, there is no need for the secondary references to cure any deficiency of Martuza.

Secondly, Applicants failed to provide any objective evidence demonstrating that the art specifically taught away from the use of mutant HSV for treating non-neuronal tumor cells. Contrary to Applicants' opinion, Martuza U.S. patent No. 5,585,096 with a filing date of June 23, 1994 specifically teaches the use of a replication-competent herpes simplex virus that is incapable of expressing both functional γ34.5 gene product and a ribonucleotide reductase for killing neoplastic cells including melanoma cells, pancreatic cancer cells, prostate carcinoma cells, breast cancer cells among others (col. 3, lines 52-58, and the title of the issued patent).

Thirdly, contrary to Applicants' belief that the U.S. Patent No. 5,585,096 merely contains unsubstantiated and speculative statements regarding to the use of a mutated HSV for killing non-neuronal tumor cells, on the basis of a similar disclosure claims specifically directed to a method of killing tumor cells (both neuronal and non-neuronal

tumor cells) in a subject using a herpes simplex virus vector comprising an alteration in the γ34.5 gene have been issued for the U.S. Patent No. 6,139,834. Without any objective evidence provided by Applicants, the issued U.S. Patent No. 6,139,834 is considered to be valid.

Fourthly, with respect to instant claims it would have been obvious to one of ordinary skilled in the art at the time of invention was made to substitute any of the mutant herpes simplex virus utilized in the method disclosed by Martuza et al. with mutant virus strain 1716 taught by MacLean et al. and Brown et al., and one of ordinary skilled in the art would have expected to successfully killing tumor cells in a subject via an intratumoral route of delivery. This is because it was already known in the art that mutant herpes simplex virus having a deletion in the γ34.5 gene has reduced non-neurovirulence and still possesses anti-neoplastic effects as exemplified by the teachings of Markert et al. and Martuza et al. Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Accordingly, claims 13 and 19-22 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Martuza et al. (U.S. Patent No. 6,139,834) in view of either MacLean et al. or Brown et al. and Markert et al. for the reasons already set forth above.

Following is a new ground of rejection necessitated by Applicants' amendment.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 and its dependent claims recite the limitation "said non-neuronal tumor cell" in line 6 of claim 22. There is insufficient antecedent basis for this limitation in the claim. Therefore, the metes and bounds of the claims can not be clearly determined.

Conclusions

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136 (a) will be calculated from the mailing date

of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Dave Nguyen, may be reached at (703) 305-2024, or SPE, Karen Hauda, at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Patsy Zimmerman, whose telephone number is (703) 308-0196.

Quang Nguyen, Ph.D.

DAVE T. NGUYEN
PRIMARY EXAMINER